Intraluminal Cervical Esophageal Perforations in Rats (Experimental Study)

Eurasian Clinical and Analytical Medicine Original Research

Cervical Esophageal Perforation

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Abstract

Aim: Esophageal perforation has high morbidity and mortality rate. Morbidity and mortality rates have been decreased slightly by the progress in surgical technics and intensive care conditions. We here aimed to search the effect of both (a) cervical esophageal perforation from anterior and lateral locations and (b) safe time interval for repair on mortality and morbidity.

Material and Methods: In our study,we have used 40 rats. The rats were first grouped into anterior and lateral perforation groups, afterwards these two groups were divided into two subgroups as early (12 h) and late (24 h) repair groups. Perforation was made with 22 gauge angiocath and repaired in early or late time periods. Before the perforation and treatment, blood samples were collected from tail vein in order to measure leucocyte levels. Blood sampled before the perforation and while sacrifying the rats-by cardiak puncture- were used to measure IL-10 levels. Contamination status were analysed and radiological studies were made. Histopathologic examination of the esophageus was made after the sacrification. In order to evaluate the rupture status in treated rats, contrast esophagograms were studied before the sacrification.

Results: The groups were evaluated according to the perforation localisation, time interval for treatment, white blood cell values revealing the infection, contamination status, IL-10 and fibrosis. We have found significant difference in white blood cell count and contamination between the rats that were perforated anteriorly, repaired early and perforated laterally, repaired in late time period. Also we have found significant difference in contamination between anterior perforation early repair group and lateral perforation early and late repair group. No statistical differences was found within the groups for IL-10, fibrosis, location of the perforation and the time of the treatment.

Discussion: As a result, we think that our findings show us anterior perforation of the cervical esophageus is better tolarated and has a wider safe time interval for treatment.

Keywords

Esophageus; Perforation; Trauma; IL-10

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Introduction

Perforation of the esophageus is a surgical emergency because of having high mortality rates [1,2]. As having no serosa, enfections can spread easily and sepsis can establish in a short period of time [3-5]. Interventional technics(tracheostomy, bronchoscopy, nasogastric tube applying, videolaryngoscopy, endoscopic esophageal instrumentations and manuplations in esophageus for neighbourhood organs (ei. Transesophageal echocardiography and ultrasound)are performed much more than before as a result of enhancements in technology and improvements in patient management. Iatrogenic injuries constitutes much of the injuries of the esophageus [2,6-8]. Most of the iatrogenic injuries those seen in cervical esophageus is caused by instrumentation [7]. As a result of this Also penetrating esophageal injuries [3,9] and perforations caused by foreign bodies are commonly seen in cervical esophageus [10]. If the injuries of the esophageus are underestimated or overlooked, mediastinitis develops and afterwards the patient dies because of sepsis [4]. There are clinic studies evaluating the esophageal perforations but none of them has a consensus on what time it is safe to perform surgery after the injury. We have planned to investigate the safe time interval for surgery.

Cervical esophageus has a special place in esophageal injuries. Because of being the narrowest and the least protected part of the esophageus, cervical esophageus is more prone to the injuries when compared to the other sides.

Surgery on time is life saving in esophageal perforations. Time interval for surgical intervention from the time of injury and the time of treatment is not well established. Knowledge about time interval was all from clinic studies.

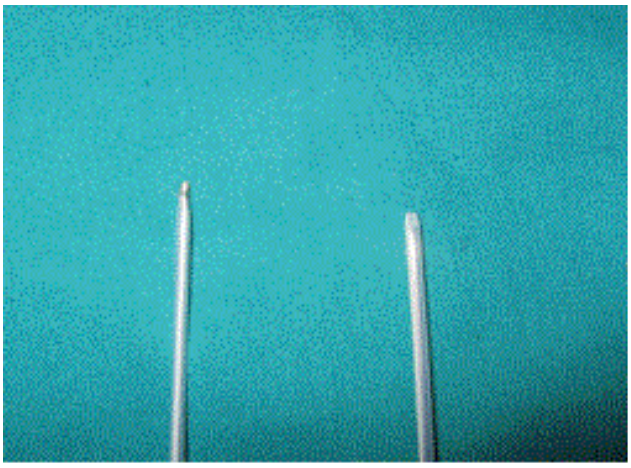
This experimental study is established to investigate the direct effect of surgery performed in different time intervals after the perforation, safe time interval for surgical treatment and the effect of perforation site which is not studied earlier.

Material and Methods

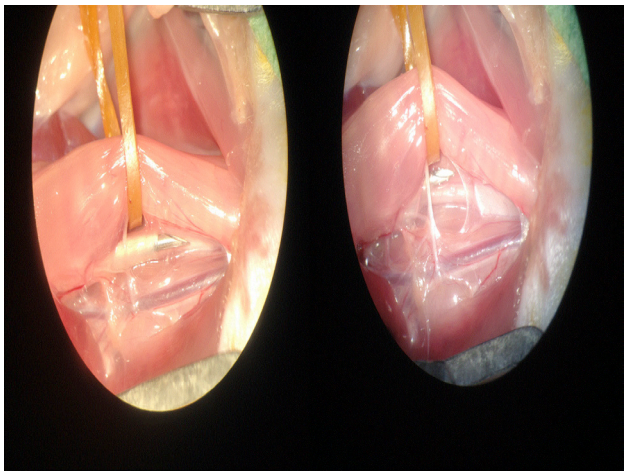
GATA ethic committee approval was taken for our study. 40 rats were used (Ratus Norvecus) in our experimental study. The rats were approximately 200-300 mg in weight and 4-6 months in age. They were first divided into two categories consisting of 20 rats according to their perforation localization whether anterior or lateral. These two groups then divided into 2 subgroups consisting of 10 rats according to their time of treatment. As a result, we have costituted 4 groups each containing 10 rats. While naming these groups we have used letter "A" for Anterior, "L" for lateral perforation, "E" for treatment after 12 hours (early) and "G" for treatment after 24 hours (late) (Figure 1).

Group "AE" refers to Anterior perforation and early treatment group. Group "AG" refers to Anterior perforation and late treatment group. Group "LE" refers to lateral perforation and early treatment. Group "LG" refers to lateral perforation and late treatment group. Anterior groups were perforated from the anterior portion, lateral groups were perforated from the lateral portion of the esophageus. Early groups were treated after 12 hours of injury with primary suturation using 7/0 absorbable material and late groups were treated after 24 hours with the same material and method.

All the rats were given anything on the day of operation. Ketamine hydrochloride (90mg/kg) and xylazine (10mg/kg) were used for anesthetics that are used parenterally (intramuscular). Before the perforation,



Picture 1. The angiocaths used for the perforation



Picture 2. Perforation of the esophageus from the lateral and anterior wall.

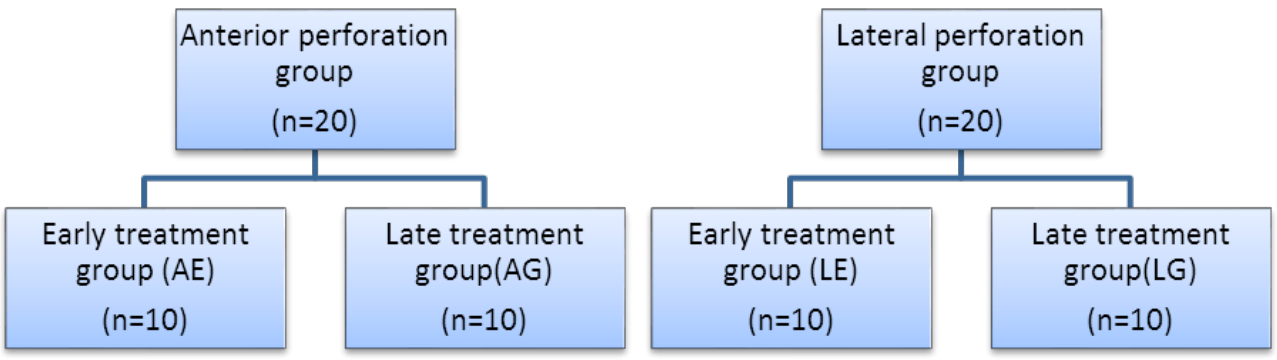
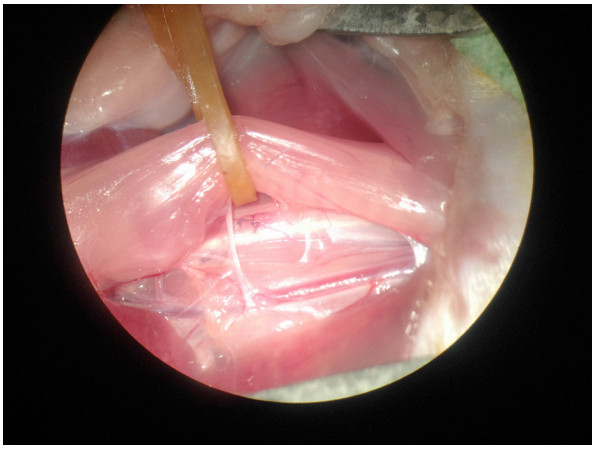


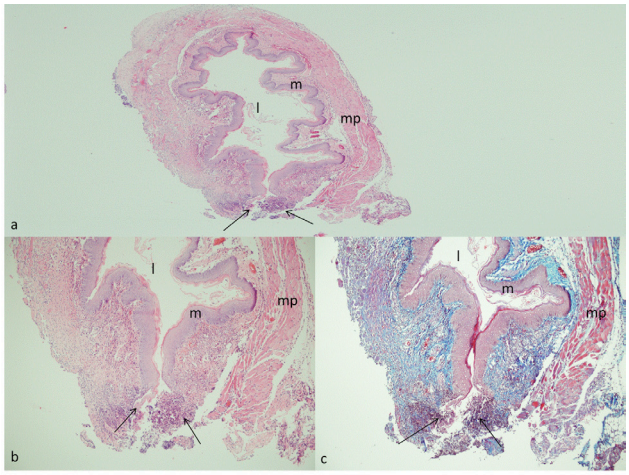
Figure 1. The Distrubition of the groups

we collect blood sample for detecting leucocyte count and IL-10 levels. After collecting the blood samples we injected same amount of serum physiologic intraperitoneally to avoid hemodynamic instability. The rats were stabilized from 4 extremities and collar region was shaved to avoid contamination. After applying antiseptic solution and aerosol designed for animals, a vertical 1,5 cm incision was made on the neck.



Picture 3. Primary suturation of the perforation site

Picture 4. Esophagograms of the rats



Picture 5. Histopathological specifications of the rupture. Continuity of the esophagus wall is absent (arrows) (a, HEx40). Intense inflammation and granulation in rupture site (arrows) (b, HEx100). Minimal fibrosis in granulation area with Trichrom stain (c, Tric.x100). (l: lumen, m: mucoza, mp: muscularis propria).

Blunt dissection was performed to lateralize the collar muscles. Once the trachea is exposed, carotis steath was dissected and put apart from the region to save these important anatomic structures while performing the perforation. Perforation is performed by 22 gauge angiocaths. 2 angiocaths were used while performing the perforation. The first one is used as a guide. In order not to make an unwanted perforation to the esophageus, we used this guide. The neddle part of the guide angiocath is cut at a distance that the metal part of it to be found in the plastic part (Picture 1). We introduce this guide orally. When we see our guide under microscope in a proper position for perforation, we changed the needle (taken from the second angiocath) to perform the perforation. The perforation was performed anteriorly in the anterior groups and laterally in the lateral groups under the microscope (Picture 2). After the perforation process, the incision was sutured without suturing of the esophageus. Depending on the groups whether early or late they were reopened for repairment of the perforated area. Before the reopening, blood from the tail is sampled to find the leucocyte count. After collecting the blood samples we injected same amount of serum physiologic in order not to make hemodynamic instability. After opening the skin incision, perforated area was washed with serum physiologic. The washed water was sent to microbiologic analyse to see if there had been any contamination or not. After washing out, the perforation was sutured by 7/0 absorbable material under a light microscope (Picture 3). The rats were fed orally after 24 hours of the operation. Parentheral analgesic and antibiotic treatment was administrated for 3 days (amoxilline 2x0.01, piralgine 0.05 cc). Before the sacrification which is performed after a week, esophagograms were studied to investigate leakage (Picture 4). The rats were sacrified by cardiak puncture. The collected blood is used to measure IL-10 levels. After the sacrification, the esophageus is excised for histopathological examination. Fibrosis, granulation tissue formation and inflammation is examined besides investigating the continuation of the lumen in histopathological examination (Picture 5). The collected blood samples are stored in the pediatric cbc tubes for leucocyte count. For IL-10 levels, the bloods were centrifuged and the plasmas were used. The specfic kit for rat IL-10 is used. The first blood samples collected are used as control group blood. All data is gathered and SPSS 15.0 is used for statistical analyse. Histopathologic, microbiologic and biochemistracal data were analysed with chi-square test as they are discrete data. Continuous data of the biochemistral data is analysed with Kruskal-Wallis test. The result $p< 0.05$ is accepted as significant.

Results

3 rats were used for study group in order to establish perforation model and treatment under light microscope. 40 rats were used for experiment groups which is divided into 4 groups containing 10 rats each. 8 rats were excluded from the study due to various reasons including severe tissue necrosis (n=3),bronchoconstriction due to tracheal strain (n= 2), sudden cardiac arrest (n= 1) and major vascular injury (n=2). As a result the number of rats in each group is shown in the first column of table 1. The avarage operation time is 25± 5 minutes.

The histopathologic examination was made by a pathologist under a light microscope blindly. The summary of histopathologic findings of the experiment can be traced on table 1.

In order to show the infection in perforation area we measured leucocyte values. The rats have broad range of leucocyte levels and do not have a treshold value for IL-10. Taking into account this knowledge, we planned to measure two times these values and compare them. Control group for leucocyte is formed by the blood samples collected before the perforation. The avarage value for the control group (8.1x 103/mm3) is compared with the second blood sample values. Second

Table 1. Histopathologic findings in the groups.

Groups	Mucosal injury n (%)	Wall injury n (%)	İnflammation		Fibrosis			Rupture n (%)
			Mild n (%)	Severe n (%)	Granulation Tissue n (%)	Mild n (%)	Severe n (%)	
AE n=7	2 (%28,5)	6 (%85,7)	1 (%14,3)	6 (%85,7)	6 (%85,7)	6 (%85,7)	1 (%14,3)	2 (%28,5)
AG n=8	1 (%12,5)	5 (%62,5)	4 (%50)	4 (%50)	5 (%62,5)	7 (%87,5)	1 (%12,5)	1 (%12,5)
LE n=8	4 (%50)	4 (%50)	5 (%62,5)	2 (%25)	5 (%62,5)	7 (%87,5)	1 (%12,5)	4 (%50)
LG n=9	4 (%44,4)	7 (%77,7)	2 (%22,2)	7 (%77,7)	7 (%77,7)	7 (%77,7)	2 (%22,2)	4 (%44,4)

Table 2. The Leucocyte status of the groups.

Groups	Leucocyte (Leu)	
	Leu> 8.1 103/mm3 n(%)	Leu< 8.1 103/mm3 n(%)
AE (n=7)	1 (%14,2)	6 (%85,7)
AG (n=8)	4 (%50)	4(%50)
LE (n=8)	4 (%50)	4 (%50)
LG (n=9)	8 (%88,8)	1(%11,1)

Table 3. The IL-10 values classified according to the control group

		Value as high-low	
		High n (%)	Low n(%)
AE (n=7)	78	3 (%42,8)	4 (%57,2)
AG (n=8)		2(%25)	6 (%75)
LE (n=8)		2(%25)	6 (%75)
LG (n=9)		6 (%66,6)	3 (%33,3)

Table 4. Microbiological analysis results of the groups

Groups	Microbiological Analysis of the Groups	
	+ n (%)	- n (%)
AE (n=7)	3 (%43)	4 (%57)
AG (n=8)	7 (%87,5)	1 (%12,5)
LE (n=8)	8 (%100)	0 (%0)
LG (n=9)	9 (%100)	0 (%0)

Table 5. Statistical results of the groups according to rupture

Groups	Rupture		P*
	+ n(%)	- n(%)	
AE (n=7)	2 (%28,6)	5 (%71,4)	
AG (n=8)	1 (%12,5)	7 (%87,5)	
LE (n=8)	4 (%50)	4 (%50)	0,38
LG (n=9)	4 (%44,4)	5 (%55,6)	

*Pearson Chi square test. AE: Anterior early (12.hour), AG: Anterior late (24.hour), LE: Lateral early (12. hour), LG: Lateral late (24.hour)

Table 6. Statistical results of the rupture absent rats according to fibrosis

Groups (n=number of rupture absense)	Fibrozis in the Rupture Negative Rats		P*
	Severe n(%)	Mild n(%)	
AE (n=5)	1 (%20)	4 (%80)	
AG (n=7)	1 (%14,3)	6 (%85,7)	
LE (n=4)	1 (%25)	3 (%75)	0,77
LG (n=5)	2 (%40)	3 (%60)	

*Pearson Chi square test. AE: Anterior early (12.hour), AG: Anterior late (24.hour), LE: Lateral early (12. hour), LG: Lateral late (24.hour)

blood sample values are classified as higher or lower than the control group. Table 2 shows the number of rats that have higher or lower values than control group.

IL-10 levels were measured in the groups from the blood samples collected before the perforation and at the time of sacrification. Control group was formed by the blood samples that are collected before the perforation. The mean value for the control group was 78 pg/ml. The values that are above this value are classified as high, below this value are low (Table 3).

Table 7. The distrubition of leucocyte values between the groups.

Groups	Leucocyte (Leu)		P*
	Leu> 8.1 n(%)	Leu< 8.1 n(%)	
AE (n=7)	1 (%14,3)	6 (%85,71)	
AG (n=8)	4 (%50)	4 (%50)	
LE (n=8)	4 (%50)	4 (%50)	0,03
LG (n=9)	8 (%88,9)	1 (%11,1)	

*Pearson Chi square test. AE: Anterior early (12.hour), AG: Anterior late (24.hour), LE: Lateral early (12.hour), LG: Lateral late (24.hour)

Table 8. Statistical Analyse of the IL-10 levels in groups

Groups	Mean value of the groups	P*
AE (n=7)	79,8	0,062
AG (n=8)	61,2	
LE (n=8)	68,6	
LG (n=9)	102,4	

*Kruskal Wallis test. AE: AE: Anterior early (12.hour), AG: Anterior late (24.hour), LE: Lateral early (12.hour), LG: Lateral late (24.hour)

Table 9. The statistical analyse of microbiological contamination

Groups	Contamination Status		P*
	+ n(%)	- n(%)	
AE (n=7)	3 (%42,9)	4 (%57,1)	
AG (n=8)	7 (%87,5)	1 (%12,5)	
LE (n=8)	8 (%100)	0 (%0)	0,006
LG (n=9)	9 (%100)	0 (%0)	

*Pearson Chi square test. AE: Anterior early (12.hour), AG: Anterior late (24.hour), LE: Lateral early (12.hour), LG: Lateral late (24.hour)

The microbiological results of the groups are shown in the table 4. All the rats in the lateral perforation groups (LE-LG) had a positive result in their cultures.

Before the sacrification, the esophagograms of the rats were performed to investigate the rupture status. The rupture was showed in 9 rats (%81.8) within 11 histopathologically confirmed ruptured rats.

Histopathologically existance of rupture is considered as fail in the treatment and absence of rupture is considered as success in treatment. When we analyse the groups by rupture, we have found no significant result within the groups (P=0.38)(Table 5). But the absence of rupture is found more in the anterior groups. Rupture absent rats in the groups were analysed according to fibrosis. The result were not statistically significant (P=0,77) (Table 6).

When we evaluated the leucocyte count statistically, we have found significance between the groups (p= 0.03) (Table 7). We have found the difference between the groups AE and LG .

The IL-10 levels were evaluated and a significant result were not found (p=0.06) (Table 8).

Microbiological analyse that showed contamination had a significant result in statistical analyse (P=0.006)(Table 9). When we examined the groups in couples we have found that groups between AE-LG and AE-LE had a significant result.

Discussion

Esophageal perforation has a high rate of mortality and morbidity. Parallel to the advences in the surgical interventions and intensive care units, mortality and morbidity rates has decreased mildly. Beside this decrease, it has a rate of % 65 in most of the centers [1,11-14]. The prognosis of the patient is strictly related to patients general status, type and the location of the injury and time interval between the injury and the time of treatment [8,15-20].

There are lots of clinical studies showing the importance of early diagnosis and treatment in esophageal perforation. Especially treatment that begins before 24 hours is told to be life saving [8,17,21-26]. Glatterer and assoc. emphasize the 16 hour for treatment in penetrating injuries of the esophageus [27]. A multicenter retrospective study from Ascensio and assoc. evaluated the effect of time loss on mortality and morbidity of the patients caused by preoperative evaluation [28]. They did not found significant difference on mortality except the complications related to esophageus. Attar and associates found a survival rate of %87 treated within 24 hours whereas % 55 treated after 24 hours [21]. Pankaj Bhatia and assoc. in their 119 patient retrospective study found the mortality was not associated with the time gap [17]. They had found the general status of the patient on admission is much more important for the complications.

The reason for different results in different papers for time interval of treatment in esophageal perforation is thought to be related with the patient selection. There can be patients with small perforations admitted after a long time and also large perforations admitted in a short time period[29]. Also we think that there can be statistical problems in equal categorisation of the patients.

In our study, we consider the existance of rupture in histopathologic examination as failure in treatment. When we evaluate the groups by rupture, we have found no statistically difference. The reason for not finding a difference between the groups is thought to be low number of rats we have. While not finding a significant difference between the groups, when we evaluate table 1 we can see that the lateral groups (early, late)have a higher number of rupture than the anterior groups. The main reason of having a low number of rupture in anterior groups is tought to be the relationship of esophageus and trachea. This relationship prevents contamination and limits the local inflammation. As a result we think that localisation of the perforation effect the result of the treatment. We have not found a significant difference in time interval by comparing the rupture. We think that if a long time pass for treatment, contamination will disseminate and afterwards inflammation in the tissue will improve leading to sepsis that will effect the treatment.

We have found a statistical difference between groups in contamination (p= 0.006). The difference was found between the anterior early group and lateral early and late group. This shows us that the perforations from the anterior aspect is less contaminated. Less contamination brings less complication, good surgical outcomes and good results in late treatments. Parallel to the contamination, leucocyte values in lateral groups is significantly higher than the anterior groups (p=0.03). This shows us the anterior perforations has a low level of contamination thus leading a less inflammation. These results reveal that perforation site is important in esophageal perforation.

There is correlation in the papers on the studies performed for the diagnosis of esophageal perforations. Direct graphies are used first following a contrast esophagograms afterwards. Esophagograms can be repeated or computed tomograms can be used if there is a suspect in diagnosis.

Onat and assoc. mentioned that the best way to evaluate the perforation is the contast esophagograms by computed tomography [3]. We have seen rupture in most of the rats (%81,8) by esophagograms which is confirmed histopathologically. Contrast esophagograms can be used in the diagnosis of esophageal perforations safely but negative results should not be thought as intact lumen.

The last period in tissue remodelling is fibrosis. Low fibrosis formation is associated with good tissue elasticity and function. Thus, we evaluated the fibrosis formation in unruptured rats. We have not found a statistically difference between the groups. All the groups had a mild fibrosis but more in anterior groups. This shows us primary suturing is healed with mild fibrosis that leads minimal loss of funcionality of the esophageus.

IL-10 is an anti-inflammatory stokin that is primarily produced from monocytes and less produced by leucocytes. Researhes revealed that IL-10 is the main immune modulator stokin in gastrointestinal system and recombinant IL-10 supress inflammation in bowels in Crohn disease [30]. We have not found significance between groups. But when we consider table 3 and 8, lateral late group has more high levels and mean value. We think that the higher IL-10 in lateral late group reveals the more severe inflammation in the lateral late group.

There are lots of papers related with esophageal perforations, however there is no consensus on the treatment of it. Non operative treatment is commonly used in iatrogenic injuries and cervical region perforations [13]. When the conservative treatment fails, surgery is then performed. This time delay prepares complications. For this reason, non operative treatment should be choosen properly to avoid such complications [31, 32]. The mainstay of the treatment is to avoid contamination and infection, rebuilding of feeding, maintenance of gastrointestinal continuing [33]. Cervical esophageal perforations and thoracal perforations that is confined by the pleural folds can be treated conservatively [34]. Gupta and Asensio had declared the main treatment in esophageal perforations is early performed surgery in their papers [28,35].

Tsalis and co-workers informed in their case report that the management protocol play an important role in the mortality rate[36]. We used the primary suturing protocol in our study. Primary suturing is commonly used in the treatment of esophageal perforations. In lateral perforations of the esophageus, we have found that lack of supportive tissue results in contamination of the mediastinum.

Before performing the lateral perforation in our study, carotid steath dissection is carried out to avoid the injury to the vessels. This dissection can be a factor for spreading the infection. Also, a laceration to the vessels can lead a hematoma in the region that compress to the vascular structures or esophageus. And also esophagovascular fistulization may occur. These complications should be kept in mind also.

Before performing the anterior perforation, we dissect esophageus from trachea in order not to injury trachea. In the perforations of the anterior esophageus, tracheal involvement must be strictly evaluated. If tracheal injury is excluded, then conservative treatment should be promptly used.

Esophageal perforation is a highly mortal and morbid injury. There is no standart treatment algorithym in perforations. Patients should be evaluated individually. In our study, we have found that anterior perforations of the esophageus is better tolarated when treated with primary suturation. Also, we have shown in our study that late recognaised anterior perforations of the esophageus has a better result from early recognaised lateral perforations. For this reason, we think that anterior perforations of the esophageus is better tolarated from the lateral perforations.

Conclusion

In our study, we have found that anterior perforations of the esophageus is better tolarated and has a wider range of time interval. We have not found a difference in time interval but we think that increased

time is associated with high rates of fail in treatment that will lead high mortality rates and complications. Our study will be supported by the experimental or clinical studies in the future.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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